REMARKS

In view of the above amendments and the following remarks, reconsideration of this application is respectfully requested.

Status of the Claims

Upon entry of the amendments presented herein, claims 1-13 and 17-20 will be pending. Claim 10 is hereby amended. Claims 14-16 are hereby canceled. Claims 1-9, 11-13, and 17-20 stand withdrawn. As set forth in the remarks below, no new matter has been added by way of the amendments to claim 10.

Maintained Rejection

35 U.S.C. § 102(e)

Claim 10 ***remains*** rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 7,186,512 to Martienssen et al. (effective filing date of June 26, 2002) ("Martienssen '512").

Claim 10 has been amended to incorporate the limitations of claims 14 and 15. Support for these amendments are found in originally filed claims 14 and 15, now canceled.

Neither claim 14 nor claim 15 was subject to this anticipation rejection based on Martienssen '512. Therefore, applicants respectfully assert that the aforementioned amendments to claim 10 are sufficient to overcome this rejection.

In view of the foregoing, applicants respectfully request that the anticipation rejection based on Martienssen '512 is improper and should be withdrawn.

New Rejections Allegedly Necessitated by Amendment

35 U.S.C. § 112, First Paragraph

Claim 16 is rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

Claim 16 has been canceled by the present amendment.

This rejection is now moot and respectfully traversed in view of the cancellation of claim 16. Therefore, applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 10, 14, and 16 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness.

With respect to claim 16, this rejection is now moot and respectfully traversed in view of the cancellation of claim 16.

With respect to claim 14, this rejection is respectfully traversed in view of the cancellation of claim 14. However, because claim 10 has now been amended to incorporate the subject matter of claim 14, further remarks rebutting this ground for rejection with respect to claim 10 are provided below.

Claim 10, as noted above, has been amended to incorporate the limitations of claims 14 and 15. In particular, the limitations of claim 14 have been inserted into subsection 3(a) of claim 10, and the limitations of claim 15 have been inserted into subsection 3(b) of claim 10.

In addition, claim 10 has been amended to limit the genomic DNA used in subsections 3(a) and 3(b) to the "genomic DNA prepared from a biological sample." Support for this amendment is found in the originally filed specification at least at paragraph [0098] beginning on page 41 and ending on page 42.

Further, claim 10 has been amended to delete subsection 3(c) thereof.

In support of this rejection, the Examiner has taken the position that one of ordinary skill in the art would not be able to determine the scope of the invention as claimed (*see*

Final Office Action, at page 8). In reply, as set forth more fully below, applicants respectfully assert that the above-described amendments to claim 10 are sufficient to overcome this ground for rejection.

First, the Examiner asserts that, since the DNA fragments as claimed must include either a "modified based" or "a base," it is not clear why the restriction enzyme must digest regardless of the presence or absence of a modification (Final Office Action, at page 8, lines 4-6 of paragraph 16). The Examiner further supports this assertion by stating that a modified base is not required by the claim.

In rebuttal, it is well known by those of ordinary skill in the art that restriction enzymes are enzymes that digest DNA sequences at specific restriction or recognition sites. These recognition sites correspond to specific nucleotide base sequences on the DNA to which a restriction enzyme binds and cleaves. A common and well-known example of a restriction enzyme is the EcoRI enzyme, which recognizes the palindromic sequence GAATTC and cuts between the guanine (G) nucleotide base and the adenine (A) nucleotide base on both the top and bottom strands, leaving an overhang (an end-portion of a DNA strand with no attached complement) of AATT on each end. The present specification (at page 11, paragraph [0028]) clearly defines the terms "base," "modified base," and "modification." In view of the specification and the common knowledge in the art, one of ordinary skill in the art would readily understand that the restriction enzyme recited in claim 10 is one that is able to digest the genomic DNA at its corresponding recognition site, whether or not the recognition site includes a modification of a base in the recognition site. In other words, the skilled artisan would understand the scope of claim 10 to mean that the restriction enzyme used is one that functions in the presence and in the absence of a modification of a base in its corresponding recognition site.

Second, the Examiner supports this rejection by stating that, because any restriction enzyme that cleaves and leaves "sticky ends" would produce a ssDNA with an exposed base, it is therefore not clear how the limitations of subsections 3(b) and 3(c) of claim 10 are limiting the claimed subject matter (Final Office Action, at page 8, lines 7-9 of paragraph 16). Again, the Examiner further supports this assertion by stating that a modified base is not required by the claim.

In rebuttal, applicants respectfully direct the Examiner to the amendments made to claim 10. As noted previously, subsection 3(b) has been amended to incorporate the limitations of claim 15. Because claim 15 was not subject to this indefiniteness rejection, this amendment is sufficient to overcome this ground for rejection as it pertains to subsection 3(b) of claim 10. Applicants also point out that subsection 3(c) of claim 10 has been deleted by the present amendments. Therefore, such amendment is sufficient to overcome this ground for rejection as it pertains to subsection 3(c) of claim 10.

Third, the Examiner asks the question whether the term "modification" includes deletions, substitutions, etc. (Final Office Action, at page 8, lines 9-10 of paragraph 16). As noted above, the specification (at page 11, paragraph [0028]) clearly defines the meaning of the term "modification" as used in the claims. One of ordinary skill, upon reading the claims in light of the specification, would readily understand the meaning and scope of the term "modification."

Fourth, the Examiner asserts that a nexus between the preamble and the last method step is missing (Final Office Action, at page 8, line 10 to page 9, line 1). Applicants respectfully disagree. The preamble of claim 10 recites a "method of analyzing a modification in a DNA to be assayed," while the last method step (i.e., subsection 3 of claim 10) recites the step of "analyzing all or part of DNA fragments contained in each of the DNA fragment groups with a DNA array." Subsection 1 of claim 10 recites that a mixture of DNA fragments is prepared from the DNA to be assayed. Therefore, it is readily apparent to one of ordinary skill in the art that the method involves analyzing a modification in a DNA to be assayed, as recited in the preamble.

Finally, the Examiner asserts that the claims are: (i) generally narrative and indefinite; (ii) fail to conform to current U.S. patent practice; and (iii) appear to be a literal translation into English from a foreign document and allegedly replete with grammatical and idiomatic errors. Applicants respectfully disagree. In view of the amendments contained herein, only claim 10 is currently pending. As amended, claim 10 is clear, definite, and contains proper use of English grammar. If the Examiner continues to maintain this ground for rejection, applicants respectfully request that the Examiner point to specific recitations in claim 10 that

allegedly contain grammatical and idiomatic errors, fail to conform to U.S. patent practice, and contain impermissible narrative or indefinite language.

In view of the foregoing, applicants respectfully assert that the rejection of claims 10, 14, and 16 for alleged indefiniteness is improper and should be withdrawn.

35 U.S.C. § 103(a)

Claims 10 and 14 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Martienssen '512 in view of U.S. Patent No. 7,247,428 to Makrigiorgos ("Makrigiorgos '428").

This rejection is respectfully traversed in view of the above amendments to the claims and the following remarks. Applicants remind the Examiner that claim 14 has been canceled, and the subject matter thereof has been incorporated into claim 10.

Applicants have already described the amendments made to claim 10, and therefore do not see the need to restate those claim amendments here.

Martienssen '512 describes a method for determining the methylation profile of individuals and a method for using those profiles to identify clones with desired traits. Martienssen '512 describes the use of restriction enzymes to produce fragmented genomic DNA. However, Martienssen '512 does not teach the use of a restriction enzyme that digests the genomic DNA in <u>both</u> the presence and absence of a modification of a base within the restriction enzyme's recognition site. Instead, Martienssen '512 (at col. 9, lines 35-64) describes using <u>either</u> a methyl-dependent restriction enzyme (i.e., that cleaves methylated sequences but not unmethylated sequences) <u>or</u> a methyl-sensitive restriction enzyme (i.e., that cleaves unmethylated sequences but not methylated sequences).

In addition to the deficiencies set forth above, the Examiner acknowledges that, unlike claim 10 of the present invention, Martienssen '512 is also deficient in that it fails to teach the use of a <u>nuclease</u> (Final Office Action, at page 10, line 16).

Therefore, the Examiner cites Makrigiorgos '428 as teaching methods for rapid screening of methylation that involve the use of treating DNA with nuclease to remove single-

stranded portions of DNA (Final Office Action, at page 10, lines17-19). It is noteworthy that the Examiner applied Makrigiorgos '428 only to claim 14, now canceled.

To further expand on the deficiencies of Martienssen '512, applicants respectfully assert that the restriction enzymes used in the methods of Martienssen '512 are different and distinct in function from those used in the present invention as claimed in claim 10.

Subsection 3(a) of claim 10 recites that the restriction enzyme is one that "can digest a DNA ***regardless of the presence or absence of a modification*** in a recognition site" (emphasis added). However, Martienssen '512 is limited to restriction enzymes that **either** (i) cleave when a base in the recognition site is modified (e.g., methylated) **or** (ii) cleave when a base in the recognition site is not modified (e.g., unmethylated). Unlike claim 10 of the present invention, Martienssen '512 does not teach or contemplate the use of a restriction enzyme that cleaves the DNA regardless of the presence or absence of a modification in the corresponding recognition site. Instead, Martienssen '512 teaches "methyl-sensitive restriction enzymes" (column 9, line 61) and "methyl-dependent restriction enzymes" (column 9, lines 59-60). The "methyl-sensitive restriction enzymes" of Martienssen '512 are different from the "restriction enzyme which can digest a DNA regardless of the presence or absence of a modification" of claim 10. Likewise, the "methyl-dependent restriction enzymes" of Martienssen '512 are also different from the "restriction enzyme which can digest a DNA regardless of the presence or absence of a modification" of claim 10, because the "methyl-dependent restriction enzymes" digest a DNA **only** in the presence of methyl-modification.

Subsections 3(a) and 3(b) of claim 10 now recite that the genomic DNA or the fragmented genomic DNAs are "prepared from a biological sample and pretreated with a ***nuclease capable of digesting a single-stranded DNA***" (emphasis added). Further, subsections 3(a) and 3(b) also recite that genomic DNA or fragmented genomic DNAs are pretreated with the nuclease:

(i) "**before** digesting the genomic DNA with the restriction enzyme" (subsection 3(a) of claim 10) (emphasis added); or

(ii) "**before** rendering the fragmented genomic DNAs fully or partially single-stranded" (subsection 3(b) of claim 10) (emphasis added).

As pointed out by the Examiner, Makrigiorgos '428 discloses S1 nuclease in column 7, line 50. However, unlike claim 10 of the present invention, in Makrigiorgos '428, the nuclease is used to cleave a DNA at the sites of mismatches of a heteroduplex which is artificially formed by hybridizing a target nucleic acid with a control nucleic acid (i.e., the wild type nucleic acid corresponding to the target nucleic acid) (*see* column 6, lines 33-55, or claims 1, 8, and 10 of Makrigiorgos '428). In contrast, the nuclease is used in the present invention to treat naturally occurring genomic DNA prepared from a biological sample. Therefore, Makrigiorgos '428 discloses the cleavage of an artificially formed heteroduplex with a nuclease, but does not disclose nor teach the cleavage of naturally occurring genomic DNA with a nuclease.

Further, nowhere does the combination of Martienssen '512 and Makrigiorgos '428 teach or suggest treating genomic DNA or genomic DNA fragments with the nuclease before digesting the genomic DNA with the restriction enzyme or before rendering the fragmented genomic DNAs fully or partially single-stranded.

In view of the above, it would not have been obvious to one of ordinary skill in the art to combine the teachings of Martienssen '512 and Makrigiorgos '428 to arrive at the presently claimed invention. Nor would it have been reasonable to believe that combining these references would have been successful in yielding the claimed method of analyzing a modification in a DNA to be assayed, without requiring undue experimentation.

For the foregoing reasons, applicants respectfully submit that the obviousness rejection of claims 10 and 14 based on Martienssen '512 and Makrigiorgos '428 is improper and should be withdrawn.

[Remainder of page intentionally left blank]

CONCLUSION

Claim 10 is now under consideration in this case. In view of the foregoing, applicants respectfully submit that the claim of the present application is in condition for allowance and such allowance is earnestly solicited.

Applicants assert that the claim amendments presented herein would not require further search or consideration on the part of the Examiner. Therefore, applicants respectfully request that the claim amendments presented herein be entered.

If any unresolved issues remain that might prevent the prompt allowance of the present application, the Examiner is respectfully encouraged to contact the undersigned at the telephone number listed below to discuss these issues.

Because this submission is being made prior to the three-month shortened statutory period for reply, no extension fee or any other fee is now due. However, the Commissioner is hereby authorized to charge any fees that may have been overlooked, or to credit any overpayments of fees, to Deposit Account No. 08-1935.

Respectfully submitted,

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By: **/Andrew K. Gonsalves/**

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